UNIVERSITI MALAYA

SYARAHAN PERDANA

GERMS AND THE HUMAN STOMACH - THE HELICOBACTER PYLORI STORY

Professor Dr. K L Goh

Universiti Malaya - Tradisi Kecemerlangan

UNIVERSITI MALAYA

GERMS AND THE HUMAN STOMACH - THE HELICOBACTER PYLORI STORY

Professor K L GOH

MB BS (Mal), FRCP (Glasg), MD (Mal), FACG, KSD

An Inaugural Lecture delivered at the University of Malaya on 5 November 1999

PROFESOR K L GOH

Profesor dan Ketua Jabatan Perubatan

BIODATA

He received his early school education in St Michael's Institution, Ipoh and La Salle, Brickfields, Kuala Lumpur. His entire secondary school education was at St John's Institution, Kuala Lumpur. He entered the Faculty of Medicine, University of Malaya in 1975 and graduated in 1980. He received his early postgraduate training in internal medicine at the University Hospital, Kuala Lumpur from 1980 to 1984. In June 1984, he passed the Royal College of Physicians examinations (MRCP) (UK). He has subsequently had training stints at the GI unit, Royal Infirmary, Glasgow and at the Department of Gastroenterology and Hepatology, Academic Medical Centre, University of Amsterdam where he worked with Professors Guido Tytgat and Kees Huibregtse.

He was appointed lecturer in Medicine at the University of Malaya in 1984, Associate Professor in June 1991 and Professor of Medicine in January 1998. In July 1998, he was appointed as Head, Department of Medicine, University of Malaya. Professor Goh is also, Head of the Division of Gastroenterology & Hepatology and Consultant in Charge of the Combined Endoscopy Unit, University Hospital, Kuala Lumpur.

Professor Goh has wide research interests in Gastroenterology, with particular focus on *Helicobacter Pylori* infection, dyspepsia and peptic ulcer disease where he has written up a thesis entitled "*H pylori* infection in Malaysia" for which he was awarded a Doctor of Medicine degree from the University of Malaya. He has published widely in many international journals in these areas. He is a faculty member of the important "Asian Pacific Consensus Meeting on *Helicobacter Pylori*" and chairman of the Malaysian Working Party on the Management of *Helicobacter pylori* infection. Professor Goh has also been a

faculty member in Working Parties on Dyspepsia and on NSAID-Asian-Pacific induced Gastropathy and invited speaker in numerous international meetings.

His special professional interest is in therapeutic endoscopy particularly in ERCPs and endoscopic treatment of oesophageal cancer. He has been an invited faculty for several international endoscopy workshops including the prestigious "Hong Kong International Workshop on Therapeutic Endoscopy" in December 1998.

Professor Goh was President of the Malaysian Society of Gastroenterology and Hepatology in 1996/7. He is a Fellow of the Royal College of Physicians, Glasgow, UK and an examiner for the MRCP (UK) examinations. He is a Fellow of the American College of Gastroenterology and is a council member of both the Asian Pacific Association of Gastroenterology and Asian Pacific Association for Digestive Endoscopy. He is an editor of the Journal of Gastroenterology and Hepatology. He is also an international editorial board member of Gastrointestinal Endoscopy and the Chinese Journal of Gastroenterology. Professor Goh was conferred the award, Kesatria Setia DiRaja, by his Majesty, the King of Malaysia, Duli Yang Maha Mulia, Yang di-Pertuan Agong in 1995.

Germs And The Human Stomach
- The Helicobacter pylori Story

by **K L GOH**

The discovery of *Helicobacter pylori,* and its association with chronic gastritis in 1983 by Warren and Marshall, ranks as one of the most important discoveries in medicine, in recent times. At the time of its discovery, no one could imagine that a bacterium could exist in the human stomach with its harsh acidic milieu of a pH of 1.2. It is known, after all, that one of the basic functions of gastric acid, is precisely, to kill off any bacteria that may enter the stomach and to protect the human host from being infected by germs. We now know, that not only does *H.pylori* exist in the human stomach but it in fact, thrives in the gastric micro-environment, where it has carved out its own special ecological niche. Once infected, unless treated, infection persists life-long in the human host.

The story of *Helicobacter pylori* was one of repeated observations over a long period of time, and one of repeated "misses" as well, until its "discovery" by Warren and Marshall in 1983. In two " back to back" letters to the editor of Lancet, Warren and Marshall described the presence of what they called "unidentified curved bacilli" and its close association with active chronic gastritis". Their first definitive paper was published a year later, also in the Lancet. In an accompanying

editorial, the paper was described as " an unusual paper from Western Australia concerning the unanswered questions surrounding peptic ulcer and gastritis." !

Germs in the human stomach have been observed for close to 100 years prior to Warren and Marshall's report. But they have been repeatedly observed, reported and then forgotten. With the advent of fibreoptic endoscopy, Steer and Colin-Jones in 1975, observed gram-negative bacilli in 80% of their patients with gastric ulcers. They thought that these bacteria were Pseudomonas and possibly contaminants and these bacteria were once again forgotten. Fung et al in 1979, a gastroenterologist working in the Royal Perth Hospital, Australia, again observed the presence of bacteria in their study entitled "Endoscopic, histological and ultrastructural correlations in chronic gastritis" which was reported in the American Journal of Gastroenterology. To their subsequent chagrin, they only made a passing reference to this observation with no comment on their possible clinical significance. They noted that many of these bacteria, although abutting directly on to the plasmalemma of the epithelial cell, were never seen within the cell and were therefore assumed to be of little significance.

Robin Warren, a pathologist working, ironically, at the same hospital as Fung in Perth, independently observed the presence of these bacteria in 1979. In his memoirs, Dr Warren recalled " In June 1979 the early days of *Helicobacter pylori* began for me. A biopsy showed severe active chronic gastritis and I saw an unusual blue line on the surface. With higher magnification I thought I could see numerous small bacilli, closely adherent to the epithelium. My colleagues did not agree until a Warthin Starry stain was very successful and showed vast numbers of bacteria."

Barry Marshall's involvement in the *Helicobacter pylori* story was entirely serendipitous. In Robin Warren's words: " I was almost

ready to publish my findings in 1981 when I met Barry Marshall, who asked to see my work. He was the gastroenterology registrar and was expected to publish a paper. Dr Marshall did not like one suggested project, so someone told him to see "that pathologist who was trying to make gastritis into a bacterial infection". The rest is history. Barry Marshall completed his Gastroenterology training in Perth, Australia and subsequently took up a job as Assistant Professor at the University of Virginia, Charlottesville, USA where he continued with numerous important studies on *Helicobacter pylori*. Barry Marshall has now returned to Perth and is Clinical Professor of Medicine at the University of Western Australia. Robin Warren has retired and is Emeritus Professor of Pathology at the same University.

H.pylori is the most common bacterial infection in the world today. It is the major cause of peptic ulcers and an uncommon lymphoma called "maltoma" (lymphoma of gastric mucosal associated lymphoid tissue). It plays a critical role in carcinogenesis of the stomach and is implicated in the pathogenesis of at least, a subset of patients with non-ulcer dyspepsia.

H.pylori is a true human pathogen. That *Helicobacter* pylori is the cause of histological gastritis is now proven beyond doubt. *H.pylori* is always present when active superficial gastritis is present. When *H.pylori* is eradicated, gastritis resolves. Koch's postulates have been proven, with Dr Barry Marshall infecting himself with *H.pylori*, developing gastritis and symptoms of acute dyspepsia. He had treatment with successful eradication of the bacteria and resolution of gastritis. Dr Arthur Morris from New Zealand, repeated the same experiment with similar disease outcome except it took him several years before he was finally cured! *H.pylori* is also not found in other types of gastritis such as autoimmune, lymphocytic and bile reflux gastritis indicating that it is not merely a commensal colonizing a

damaged mucosa. The association of chronic gastritis with peptic ulcer had been known for a long time, before the discovery of *H.pylori*. But the association between the two was not clear until the discovery of the association between *H.pylori* and gastritis.

While the Royal Perth Hospital will always remains the home of *H.pylori*, many groups around the world were more involved in scientific research in gastric diseases at that time and were quick to get involved in *H.pylori* research. One such center is in Amsterdam. Guido Tytgat, an eminent gastroenterologist, has been in the forefront of gastrointestinal research since the early 70's when he became Professor and Head of the Department of Gastroenterology at the Academic Medical Center, University of Amsterdam. His group pushed very hard and quickly in *H.pylori* research and in 1990 published their paper entitled "Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*" in the Lancet. In an earlier paper in 1989, with Eric Rauws as first author, Tytgat and colleagues were the first to describe resolution of gastritis on long term follow-up following *H.pylori* eradication.

Many studies have now supported these early findings and we now know that eradication of the bacteria results in abolition of relapse of peptic ulcer disease. The older textbooks of medicine frequently state that " duodenal ulcer disease is a chronic relapsing disease which will eventually burn out with time". This is no longer true as we can now cure the disease. This is indeed a dramatic and remarkable discovery in medicine. With the great impetus to treat the infection world wide, it is not impossible to imagine that in the not too distant future, peptic ulcer disease may become a disease we read about rather than treat !

Observations of a high prevalence of *H.pylori* in patients with gastric and duodenal ulcers have been universal. We have shown in one of our studies that *H. pylori* eradication alone without continued

conventional ulcer treatment, resulted in healing of ulcers. Zheng and collegaues (1985) from China and Lam and colleagues (1997) from Hong Kong, have demonstrated ulcer healing with antibiotics alone. Other studies have also shown that *H.pylori* infection preceded ulcer disease temporally, thus making it biologically plausible that *H.pylori* is aetiologically related to ulcer disease.

For a while it became a norm to attribute every disease of the stomach to *H.pylori*. Non-ulcer dyspepsia (NUD) has always been a difficult clinical problem. But the causal association of this syndrome with *H.pylori* has not been established. NUD studies are difficult to perform and fraught with pitfalls. *H.pylori* has not been shown to be more common in NUD patients compared to healthy controls, there are no specific *H.pylori* related dyspeptic symptoms, there are no clear-cut pathogenic mechanisms by which *H.pylori* infection can result in dyspepsia and eradication studies have not consistently resulted in improvement in symptoms.

Current interest and "anxiety" is focussed on the role of *H.pylori* in gastric carcinogenesis. Ecological comparisons have shown that areas with high rate of gastric cancers were also areas with a high prevalence of *H.pylori*. Compelling examples can be seen in the South American countries and in certain regions in China. The first strong evidence supporting the role of *H.pylori* in gastric carcinogenesis came about in 1991. Abraham Nomura and colleagues from Hawaii published results of a nested case-control study. In this study, a large group of Japanese American men were conscripted into the military in 1942, a year after the Pearl Harbor bombing. In the 1960's an extensive health survey was carried out on these men who were born between 1900 and 1919 and 8000 subjects had blood samples taken. Between 1968 and 1989, 137 of this group of men had developed gastric cancer. Nomura and colleagues focussed on a group of 109 cancer patients and studied a matched group of healthy subjects from this cohort. They found that

those who were *H.pylori* positive (on bloods taken 20 years previously) had a six-fold increased risk of developing gastric cancer. Similar studies were performed by Julie Parsonnet and her group from Stanford and David Forman of the Imperial Cancer Research Fund in London. In both of these studies, an increased risk of cancer in the presence of *H.pylori* infection were also noted. Pelayo Correa in 1992, modified and proposed a model of human gastric carcinogenesis as a multi-step, multifactorial process with *H.pylori* infection as the initiating event. In June 1994, the International Agency for Research in Cancer, an arm of the World Health Organisation declared *H.pylori* as a Class 1 (definite) carcinogen.

The news of the discovery of *H.pylori* and its possible clinical significance did not come with a "bang". In fact, for several years following its discovery, doctors continued to view it with great scepticism. We started our work at the University Hospital quite modestly, in 1985. At that time, *H.pylori* was diagnosed histologically. A preliminary report, was presented at the Annual Society of Pathology Conference in 1986 and I subsequently, presented results on a larger group of patients at the Malaysia Singapore Congress. Our initial observations on racial differences were published as a full a paper in 1990 in the Journal of Gastroenterology and Hepatology at the same time as JY Kang and colleagues from Singapore had their report published in the Gut. We performed a pain-staking trial on non-ulcer dyspepsia and *H.pylori* in 1988-89 and were rewarded with its publication in the Scandinavian J Gastroenterology in 1991. For many years, this paper was widely quoted. A subsequent paper on gastric emptying and non-ulcer dyspepsia has also been published.

In 1990, we were performing clinical trials with the new acid-suppressing drug omeprazole. We had then started to perform, routine urease tests (for *H.pylori* infection) on gastric biopsies of all patients undergoing endoscopy. I observed that patients who were treated with

omeprazole, always tested negative with the urease test. ASTRA Pharmaceuticals (makers of omeprazole) were sceptical of the effect of their drug on *H.pylori*, although preliminary reports from Europe had already been published. Together with my colleagues, Pit Anderson and KK Tan, we sent a letter to the American Journal of Gastroenterology and entitled it "Omeprazole kills *H.pylori*". Martin Floch who was editor then, accepted the letter but insisted we change the title to "Omeprazole may kill *H.pylori*". Again, the discovery of the effect of omeprazole on *H.pylori* was completely serendipitous. Proton-pump inhibitors have now become the cornerstone of treatment of *H.pylori* infection. In combination with antibiotics it has proven to be highly efficacious. We published a definitive paper in 1994 in the American Journal of Gastroenterology, entitled "Omeprazole 40mg om combined with amoxycillin alone or with amoxycillin and metronidazole in the eradication of *Helicobacter pylori*". Since then, our GI research team has gone on to perform numerous clinical trials testing various combinations of drugs on more than 600 patients with *H.pylori* infection. Our observations have contributed greatly to the understanding of not just the efficacy of drugs but of ulcer healing, cost-effectiveness of treatment and bacterial resistance to antibiotics: metronidazole and clarithromycin particularly in the local context.

I presented our paper on zero reinfection rate at the American Digestive Disease Week (DDW) in 1995 in San Diego and it attracted much attention as most workers in the Western world were sceptical that treatment was worthwhile in areas of the world where there was high prevalence of *H.pylori* and presumably a high reinfection rate. Our definitive paper on reinfection was published in the European Journal of Gastroenterology and Hepatology and subsequently several reports from the Asian-Pacific area have supported our observations. We have now followed our initial cohort of patients endoscopically, for more than 5 years and we have continued to observe a very low reinfection

rate. Additionally with reports of occurrence of gastroesophageal reflux (GORD) following eradication, we looked specifically for occurrence of new symptoms particularly those related to GORD and for endoscopic evidence of oesophagitis. In a report at the American Digestive Disease Week 1999, we observed extremely low incidence of oesophagitis and GORD symptoms amongst our patients.

Observations of the low prevalence of peptic ulcers disease and cancer of the stomach amongst Malays have been known since the 1960s. In our early observations and report in 1990 as well as in Kang's report in the same year, a low prevalence of *H.pylori* amongst Malays were reported. Uyub and colleagues in 1994 reported on an inordinately low prevalence of *H.pylori* amongst Kelantanese Malays. As part of my Doctor of Medicine thesis, serum from several parts of the country were tested for *H.pylori* antibodies. In keeping with our earlier notion, Malays consistently had lower prevalence rates compared to the other major races: Indians and Chinese. In areas of high prevalence for example in Kota Kinabalu, Sabah, the prevalence in Malays is relatively higher but still lower compared to the other racial groups. In a large prospective endoscopy survey, performed on 1060 patients, at the University Hospital, Chinese race and Indian race were found to be significant independent risk factors, following multivariate analysis using multiple logistic regression analysis.

The marked differences between the three major races particularly in West Malaysia points to a racial cohort phenomenon. Our hypothesis of a *racial cohort* phenomenon is based on the presumption that Chinese and Indians, started off originally with a large reservoir of the infection, at the time of immigration to Malaysia more than 100 years ago. This is suggested by the high prevalence of *H.pylori* in their countries of origin. The Malays, on the other hand are a relatively, "*H.pylori* free" race. There has been only a low level of trahsmission of infection between races over time, although all 3 major

races have lived together for close to two generations. The reason that the infection is confined to a racial cohort, suggests that transmission of infection requires close contact, as in within families and within racial groups. While there is much casual social interaction between races, it is noteworthy that intermarriage between races is not commonplace in our local population. These racial differences, are further underlined in a serological study in Malaysian children that we performed, where Chinese and Indian children, were found to have significantly higher *H.pylori* prevalence compared to Malays.

Differences in incidence rates of peptic ulcer disease and cancer of the stomach between races are further intriguing. While Indians have as much *H.pylori* infection as Chinese, the incidence of peptic ulcer and cancer of stomach are much lower than for Chinese. Herein lies the Indian enigma. The differences in clinical outcome may be related to differences in infecting strains or differences in the host particularly with respect to acid-secreting capacity or differences in environmental factors between the races. A multiracial society, where three major Asian races live side by side, provides a living experimental model to further understand mechanisms of disease causation associated with *H.pylori* infection.

The *H.pylori* story has taught us several important lessons: the cause of two important diseases-peptic ulcer and gastric cancer, arose from simple observations and unsophisticated clinical studies, lack of understanding of an observation does not mean insignificance of that observation and should instead be a spur for more research, a disease is not conquered until its underlying cause is discovered, however well one may be able to control it- the case in point being peptic ulcer disease.

For me, my interest in *H.pylori* has stretched over 15 years. In this time, it has provided me with the opportunity, not just for a

scientific endeavor but it has been a maturing experience, in other ways as well. I have worked for and obtained a Doctoral degree from the University of Malaya and I have learnt many research methods, which will now be invaluable, particularly to younger clinical researchers.

H.pylori research has now moved on into an accelerated new phase with the discovery of its exact genomic sequence. *H.pylori* is now a major interest of molecular biologists, where exciting work is being done to identify " good" strains and bad "strains". Work continues to help us understand further host immune responses and to identify environmental factors, which may modulate disease outcome. Much work has been done on the development of a therapeutic vaccine and new targets for therapy. Further work has also identified not just non-*H.pylori* gastric bacteria but Helicobacter species in other parts of the gastrointestinal tract and in the biliary tree.

Internationally, *H.pylori* is a growth industry for several pharmaceutical companies. "Helicobacter" is a Journal and *H.pylori* has its own international conferences. In 1998, the Malaysian Society of Gastroenterology and Hepatology hosted the 2nd Western Pacific Helicobacter Congress, which turned out to be a very successful meeting. Several Consensus panels in the North America, Europe and Asia have been convened and guidelines for diagnosis and treatment have been drawn up.

FURTHER READING

- Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; i:1273-1275 (letters).

- Marshall B, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; i:1311-4.

- Fung WP, Papadimitriou JM, Matz LR. Endoscopic, histological and ultrastructural correlations in chronic gastritis. Am J Gastroenterol 1979; 71:269-79.

- Goh KL, SC Peh, NW Wong, N. Parasakthi, SD Puthucheary. *Campylobacter pylori* infection - Experience in a Multiracial population. J Gastroenterology and Hepatology 1990; 5:277-80

- Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. Lancet 1990;335:1233-5.

- Goh KL, Parasakthi N, Peh SC, Wong NW, Lo YL, Puthucheary SD. *Helicobacter pylori* infection and non-ulcer dyspepsia: the effect of treatment with colloidal bismuth subcitrate. Scand J Gastroenterol 1991.26:1123-31

- Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Eng J Med 1991; 325:1132-36.

- Goh KL, Tan KK, Anderson PE. (1991) Omeprazole may kill *Helicobacter pylori*. Am J Gastroenterol; 1991: 86:124 (letter).

- Goh KL, Peh SC, ParasakthiN, et al. Omeprazole 40mg om combined with amoxicillin alone or with amoxicillin and metronidazole in the eradication of *Helicobacter pylori*: results of a prospective, controlled and randomized trial with long-term follow-up. Am J Gastroenterol 1994;89:1789-92.

- Goh KL, N Parasakthi, Peh Sc et al., *Helicobacter pylori* eradication with short course therapy leads to duodenal ulcer healing without the need for continued acid-suppression therapy. European J Gastroenterol Hepatol 1996; 8:421-3.

- International Agency for Research on Cancer. Schistosomes, liver flukes and *Helicobacter pylori*. IARC monographs on the Evaluation of Carcinogenic Risks to Humans. 1994; Vol 61. Lyon, France: IARC.

- Goh KL, N Parasakthi, SC Peh . Reinfection and ulcer relapse in South-East Asian patients following successful *Helicobacter pylori* eradication: Results of a two year follow-up. Eur J Gastroenterol Hepatol 1996; 8:1157-60.

- Goh KL. *Helicobacter pylori* infection in Malaysia. Doctor of Medicine Thesis, 1996, University of Malaya.

- Warren JR. Discovery and pathology of *Helicobacter pylori*. (Personal memoirs). Proceedings BYK-Gulden Symposium, Xth International Workshop on Gastroduodenal Pathology and Helicobacter pylori, 1997:7-13.

- Lam SK, Ching CK, Lai KC, Wong BCY, et al. Does treatment of *Helicobacter pylori* with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study. Gut 1997; 41: 43-8.

- Goh KL, Parasakthi N, Chuah SY, Cheah PL, Lo YL, Chin SC. One-week low dose triple therapy with proton-pump inhibitors - optimal therapy for *H.pylori* eradication ? Alim Pharm Ther 1997; 11: 1115-8.

- Tomb JF, White O, Kervalage AR, et al. The complete genome sequence of the gastric pathogen *Helicobacter pylori*. Nature 1997; 388:539-47.

****